III. Remarks

A. Amendments to the Claims

Applicants have amended claims 8–9 and 13–14 to further define the water-soluble polymeric protective colloid used to stabilize the claimed calcium salt against agglomeration by deleting from the group of colloids, albumin and water-soluble derivatives of water-insoluble natural polymeric substances. As the protective colloids now set forth in claims 8–9 and 13–14 are included in the listing of protective colloids previously set forth in those claims prior to the amendment, support for the newly amended claims is provided by the claims prior to the amendment.

Claims 11–12 and 18–19, which had been withdrawn, are now canceled in order to place the application in condition for allowance in the event that the pending rejections under 35 U.S.C. Sections 112 and 103 are withdrawn.

B. Rejections Under 35 U.S.C. Section 112

1. **Claims 8–10 and 13–14 are rejected under 35 U.S.C. Section 112, first paragraph, as failing to comply with the written description requirement;**

2. **Claims 8–10, 13–17 and 20–21 are rejected under 35 U.S.C. Section 112, first paragraph because the specification, while considered as enabling for suspensions of nanometric particles with certain adsorbants "does not reasonably provide enablement for suspensions of nanometric particles surface-treated with other types of adsorbants" (Action at page 3, lines 16–17); and**

3. **Claims 8–10 and 13–14 are rejected under 35 U.S.C. Section 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.**

These rejections specifically object to the inclusion as protective colloids of "water-soluble derivatives of polymeric natural substances," which was set forth in claims 8–9 and 13–14 (*See* Action at page 3, lines 5–11, page 5, lines 13–16 and page 7, lines 8–16). Applicants have amended claims 8–9 and 13–14 to delete this term. As the remaining claims, 10, 15–17 and 20–21 cited in the rejections are dependent upon one of claims 8–9 or 13–14, or upon a claim that is dependent ultimately upon claim 9, claims 10, 15–17 and 20–21 are also no longer directed to protective colloids comprising "water-soluble derivatives of polymeric natural substances."

Accordingly, by reason of the aforesaid amendment to claims 8–9 and 13–14, the rejections under 35 U.S.C. Section 112 are believed to have been rendered moot and should be withdrawn.

C. Rejection Under 35 U.S.C. Section 103

Claims 8–10, 13–17 and 20–21 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over United States Patent No. 6,919,070 to Rudin et al., in view of Japanese Patent Document 6-329,557 to Ouda et al. (English language translation).

1. The Examiner's reasons for the rejection are set forth in the Action at page 9, lines 4–23, and are as follows:

> The primary reference discloses remineralizing toothpastes (column 1, lines 19–38) comprising 1 to 50, preferably 2 to 20 percent by weight (column 1, lines 58–63(nanometric hydroxyapatite particles having rod-like (anisotropic) dimensions, *i.e.*, diameters of 1 to 100nm and lengths of 10 to 200nm; see the abstract. The toothpastes contain various conventional ingredients, including up to 25 percent by weight silica abrasives (column 3, lines 48–52) and up to 5 percent by weight nonionic surfactants (column 3, lines 38–41). The reference differs from the instant claims insofar as surface-treatment is not specified, although the reference clearly teaches at column 3, lines 11–15 that "the product will comprise a liquid phase containing humectants and binding thickeners which act to maintain

the particulate solid abrasive and HA crystals in the form of stable suspension in the liquid phase" (emphasis added).

The secondary reference teaches that stability of hydroxyapatite suspensions can be improved by surface treating the particles with albumin or a polycarboxylic acid. The optimal proportion of surface treating agent was found to be 5 percent by weight, based on the weight of the hydroxyapatite particles (paragraph 0023). Although nanometric particles are disclosed (see paragraph 0009, for example), the prior art differs from the instant claims insofar as it does not specify "rod-like" (anisotropic) particles.

It would have been obvious to have surface-treated the hydroxyapatite particles of the primary reference suspensions albumin or a polycarboxylic acid, motivated by the desire to improve suspension stability as taught by the secondary reference.

2. Comparison of claimed invention with Rudin et al. and Oda et al.

The comparison of Applicants' claimed invention with the subject matter disclosed in Rudin et al. and Oda et al. is being made in association with a Second Declaration of Dr. Christian Kropf, which is attached hereto as **EXHIBIT A**. Dr. Kropf is one of the inventors of this application.

Claim 8 of the application is directed to a suspension. The remaining claims 9–10, 13–17 and 20–21 are directed to a toothpaste comprising the suspension, a method of remineralizing teeth comprising the suspension, or other suspensions within the scope of claim 8. Claim 8 reads as follows:

Claim 8. A suspension of one or more phosphate calcium salts, fluoride calcium salts, or flurophosphate calcium salts in a liquid medium in which the salts are less than 1 g/l soluble, wherein the calcium salts comprise primary particles having diameters of from 5 to 50 nanometers and lengths of from 10 to 150 nanometers, stabilized against agglomeration by a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble surfactant or of a water-soluble polymeric protective colloid selected

from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropyl guar, adsorbed onto said particles.

(Second Declaration of Kropf, Paragraph 4).

The Rudin et al. patent discloses a composition characterized in that it comprises particles of hydroxyapatite with an average particle size in length (l), width (d), and thickness (h). The values for these dimensions are: (l) from 0.2 μm to 0.01 μm, (d) 0.1 μm to about 0.001 μm and (h) from 0.1 μm to 0.0001 μm (column 2, lines 22–27). (Second Declaration of Kropf, Paragraph 5).

Rudin et al. further discloses that the hydroxyapatite being introduced into the composition possesses osteo-reparative properties and contains preferably about 100% $Ca_{10}(PO_4)_6(OH)_2$ and that the specific surface of hydroxyapatite used in the composite advantageously is 100 to 150 m^2/g (column 2, lines 41–45). This disclosure indicates that the hydroxyapatite disclosed in Rudin et al. is pure hydroxyapatite. (Second Declaration of Kropf, Paragraph 6).

Rudin et al. further discloses an oral product that will comprise a liquid phase containing humectants and binding thickeners which act to maintain the particulate solid abrasive and hydroxyapatite crystals in the form of stable suspension in liquid phase (Column 3, lines 11–15). On the basis of the disclosure in Rudin et al., the hydroxyapatite crystals in the suspension are pure hydroxyapatite. (Second Declaration of Kropf, Paragraphs 6 and 7).

The conclusion that the hydroxyapatite particles disclosed in Rudin et al. are pure is further based on the disclosure at column 2, lines 46–51 of Rudin et al. that U.S. Patent No. 6,254,855 B1 describes a method for producing a suspension of hydroxyapatite as described in the Rudin et al. application. U.S. Patent No. 6,254,855 B1 discloses in Example 1 that according to the method described in that patent, a pure stochiometric hydroxylapatite in a suspension form is produced free of admixtures (Column 3, lines 43–67). (Second Declaration of Kropf, Paragraph 8).

The calcium particles claimed in Claim 8 of the application are not pure hydroxyapatite. They are particles of calcium salt with a water-soluble surfactant or colloid selected from a group of water-soluble protective colloids adsorbed onto said particles. Accordingly, the particles claimed in the application are different in composition than the pure hydroxyapatite particles disclosed in Rudin et al. (Second Declaration of Kropf, Paragraph 9).

A comparison of the suspension claimed in Claim 8 with the suspension disclosed in Rudin et al. reveals that the claimed suspension is distinct from the suspension taught or suggested by Rudin et al. Rudin et al. discloses crystals of pure hydroxyapatite of a defined particle size that are maintained in a suspension. Applicants' claimed suspension is of particles of calcium salts, wherein a water-soluble surfactant or defined water-soluble polymeric protective colloid is adsorbed onto said particles. Accordingly, Rudin et al. does not disclose or suggest Applicants' claimed suspension comprising particles of one or more calcium salts with a defined surfactant or colloid adsorbed onto said particles, which is set forth in all of Applicants' pending claims 8–10, 13–17 and 20–21. (Second Declaration of Kropf, Paragraph 10).

Oda et al. relates to a carrier for absorbing a biologically active substance and medicinal preparation in which a biologically active substance is absorbed by this carrier (Paragraph [0001]). The Oda et al. invention is directed to a carrier for absorbing a biologically active substance comprising fine particles of hydroxyapatite with an average particle diameter of 500 nm or less surface-processed with albumin and/or a polyhydric organic acid (Paragraph [0006]). (Second Declaration of Kropf, Paragraph 11).

In Working Example 1 of Oda et al., fine particles of hydroxyapatite are surface treated with human serum albumin and low molecular weight gelatin in concentrations of 0.5 mg/ml, 1.5 mg/ml and 4.5 mg/ml (all aqueous solutions) (Paragraph [0017]). The dispersion of the surface-treated hydroxyapatite fine particles was measured using a granularity distribution measuring device (Shimazu Works) and the average particle diameter was determined. The effect of the human serum albumin and low molecular weight gelatin on the dispersion is shown in Table 1 on page 8 of the English text (Paragraphs [0018]–[0019]). (Second Declaration of Kropf, Paragraph 12).

Oda et al. then discloses that according to the data set forth in Table 1, it is clear that the average particle diameter of the particles with human serum albumin was 100 nm or

less, and that there was no aggregation and good dispersion properties no matter how much was added. When the low molecular weight gelatin was added, aggregation occurred and approximately 80% had an average particle diameter of 500 nm or more no matter how much was added (Paragraph [0020]). (Second Declaration of Kropf, Paragraph 13).

The result disclosed in Oda et al. teaches away from Applicants' claimed suspension of particles "stabilized against agglomeration by a content of at least 0.01% by weight, based on the weight of the suspension, of a water-soluble surfactant or of a water-soluble polymeric protective colloid selected from the group consisting of gelatin, casein, starch, plant gums, cellulose ethers, methylcellulose, hydroxyethylcellulose, carboxymethylcellulose, hydroxyethylstarch and hydroxypropyl guar, adsorbed onto said particles. In other words, Applicants' claimed suspension may include gelatin but does not include albumin or a polyhydric organic acid. In contrast, one of ordinary skill in the art of the subject matter of Applicants' invention relying on the teaching in Oda et al. that "when gelatin was added, aggregation occurred and approximately 80% had an average particle diameter of 500 nm or more no matter how much was added" would conclude that gelatin is unsuitable for stabilizing particles of hydroxyapatite against agglomeration. Accordingly, one of ordinary skill in the art could not derive Applicants' claimed suspension of particles from Oda et al. (Second Declaration of Kropf Paragraph 14).

For the reasons set forth above, the Rudin et al. and the Oda et al. suspensions of particles are distinct from Applicants' claimed suspension of particles of calcium salt wherein a water-soluble surfactant or water-soluble polymeric protective colloid, as defined in Applicants' Claim 8, is adsorbed onto said particles. Indeed, Oda et al. teaches away from attempting to adsorb gelatin onto the Oda et al. particles. Accordingly, Oda et al., like Rudin et al., does not disclose or suggest Applicants' claimed suspension comprising particles of calcium salt with a surfactant or colloid as defined in Claim 8 adsorbed onto said particles, which is set forth in all of Applicants' pending claims, 8–10, 13–17 and 20–21. (Second Declaration of Kropf, Paragraph 15).

3. Legal standard to be applied in obviousness rejections

The rejections under 35 U.S.C. Section 103 are addressed in Section 2141 of the Manual of Patent Examining Procedure. This section begins with an analysis of the *Graham* factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966).

Section 2141 contains the following statement under the heading "Basic Considerations Which apply to Obviousness Rejections ."

> When applying 35 U.S.C. Section 103, the following tenets of patent law must be adhered to:
>
> (A) The claimed invention must be considered as a whole;
>
> (B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
>
> (C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
>
> (D) Reasonable expectation of success is the standard with which obviousness is determined.
>
> *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n. 5, 229 USPQ 182, 187 n. 5 (Fed. Cir. 1986).

Section 2141 also includes under a subsequent heading entitled "Objective Evidence Must Be Considered," a statement which is quoted in pertinent part:

> Objective evidence or secondary considerations such as unexpected results, commercial success, long-felt need, failure of others, copying by others, licensing and skepticism of experts are relevant to the issue of obviousness and must be considered in every case in which they are present. When evidence of any of these secondary considerations is submitted, the Examiner must evaluate the evidence. The weight to be accorded to the evidence depends on the individual factual circumstances of each case. *Stratoflex, Inc.*, v. *Aeroquip Corp.*, 713 F.2d 1530, 218 USPQ 871 (Fed. Cir. 1983); *Hybritech, Inc., v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987). The ultimate determination on patentability is made on the entire record.

In re Oetiker, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

As noted above in Section 2, a comparison of the claimed invention as a whole as set forth in claim 8 and the Rudin et al. and Oda et al. references considered as a whole demonstrates that Rudin et al. and Oda et al. do not disclose, exemplify or even suggest Applicants' claimed invention or the desirability of making Applicants' claimed invention. Neither Rudin et al. nor Oda et al. discloses Applicants' claimed particles of defined calcium salts with a water-soluble surfactant or a water-soluble polymeric protective colloid selected from a defined group of water-soluble polymeric protective colloids adsorbed onto said particles. Instead, Rudin et al. discloses pure hydroxyapatite particles. In Applicants' claimed invention the water-soluble polymeric protective colloid is selected from the group including gelatin. Oda et al. discloses that the use of low molecular weight gelatin for the purposes of providing a dispersion of surface-treated hydroxyapatite fine particles resulted in the aggregation of the particles and eighty percent of the particles having an average particle diameter of 500 nm or more, no matter how much gelatin was added (*See* Paragraphs [0018] to [0020] of Oda et al.). In contrast, Applicants' claimed particles have diameters of 5 to 50 nanometers. Applicants' disclosure of a claimed suspension of one or more calcium salts in a liquid medium stabilized against agglomeration by a content of a water-soluble polymeric protective colloid selected from a group including gelatin constitutes an unexpected result relative to the disclosure in Oda et al. that the use of gelatin agglomerated fine particles of hydroxyapatite in a suspension. Such an unexpected result constitutes objective evidence that further supports the unobviousness of Applicants' claimed invention over the disclosure in the Oda et al. patent.

In summary, Applicants' claimed suspension comprising particles of a calcium salt with a water-soluble surfactant or colloid selected from a group of water-soluble protective colloids adsorbed onto said particles is different in composition from the pure hydroxyapatite particles disclosed in Rudin et al.

In addition, Applicants' claimed suspension of particles of a calcium salt with a surfactant or colloid selected from a group of water-soluble protective colloids including gelatin is unexpectedly different from the carrier for adsorbing a biologically active substance disclosed in Oda et al., which comprises fine particles of hydroxyapatite that cannot be maintained in a suspension with a gelatin colloid without becoming agglomerated. Hence, using the basic considerations which apply to obviousness rejections, and the standard for objective evidence set forth in Section 2141 of the Manual of Patent Examining Procedure, there exists no *prima facie* case of obviousness of Applicants' claims 8–10, 13–17 and 20–21 over the combination of Rudin et al. and Oda et al. Accordingly, the rejection of claims 8–10, 13–17 and 20–21 as being unpatentable over United States Patent No. 6,919,070 to Rudin et al. in view of Japanese Patent Document 6-329,557 to Oda et al. is untenable and should be withdrawn.

IV. Conclusion

It is believed that the above Amendment and Remarks constitute a complete response under 37 C.F.R. § 1.111 and that all bases of rejection in the Examiner's Action have been adequately rebutted or overcome. A Notice of Allowance in the next Office Action is, therefore, respectfully requested. The Examiner is requested to telephone the undersigned attorney if any matter that can be expected to be resolved in a telephone interview is believed to impede the allowance of pending claims 8–10, 13–17 and 20–21 of United States Patent Application Serial No. 09/868,379.

Respectfully submitted,

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